REMARKS / ARGUMENTS

Upon entry of the present amendments, claims 35, 38 and 39 are pending in the application. Claims 1-29 and 31-34 are withdrawn from consideration. Claim 30, 36 and 37 are cancelled without prejudice. New claims 38 and 39 have been added. Support for amended claim 35 and new claim 38 appears at least in original claim 1 and claim 3 as well as at page 4, lines 21-30 through page 6, lines 1-15; page 10, lines 24-32 through page 11, lines 1-16 and page 19, line 10 and Figures 4-11 in the specification as originally filed. Support for new claim 39 appears at least at page 6, lines 10-15 and Figures 4-11 in the specification as originally filed. The foregoing amendments were made without any intention to abandon any subject matter, but with the intention that one or more claims of the same, lesser, or greater scope may be pursued in a later application or in a continuation, continuation-in-part, or divisional application. The present amendment does not add new matter.

The following remarks are responsive to objection/rejections raised by the Examiner in an Office Action, dated February 21, 2006, which was made final.

Claim Rejections -35 U.S.C. § 112, first paragraph

The Examiner rejected claim 35-37 pursuant to 35 U.S.C. §112, first paragraph as indefinite for failing to particularly point out and distinctly claim the subject matter the Applicants regard as their invention. Specifically, the Examiner alleges that, the specification as filed does not provide a written description for the breath of the subject matter claimed. The Applicants traverse the Examiner's rejection of claims 35-37 as this rejection is mooted by the amendment of claim 35 and cancellation of claims 36-37 by present amendment.

Claim 35 as amended is directed to a method of treating a patient with a tumor comprising drug-resistant tumor cells mediated by p-glycoprotein pump, by administering a compound to the patient which has a formula W-Z-X. The claim recites that X is a chemotherapeutic agent (doxorubicin or paclitaxel); W is a monoclonal antibody which selectively binds to a polypeptide expressed on the surface of the tumor cells; and Z is a breakable linker which covalently links W and X together, wherein said W, when linked to Z, remains available for binding to the tumor cells, the breakable linker being cleavable in the tumor cells for releasing X into the tumor cells. The release of X into the tumor cells is cytotoxic to the tumor cells, thereby treating the patient. The Applicants submit that the specification as filed teaches how to make and use compounds of the invention in which doxorubicin and

paclitaxel are the chemotherapeutic agents. Further, as the Examiner points out, the specification as filed provides written description for compounds of the invention comprising monoclonal antibodies directed to p75 neurotrophin receptor (p75), neurotrophic tyrosine receptor kinase (TrKA) or insulin-like growth factor receptor, type 1 (IGF-1R) polypeptide. (Office Action at page 6, lines 10-12). For example, the invention provides for monoclonal antibody such as α-IR3; 5C3; and MC192, which are directed to these polypeptides and to which new claim 39 is specifically directed. The Applicants have demonstrated the utility of compounds of the invention which include monoclonal antibodies directed to p75 neurotrophin receptor (p75), neurotrophic receptor tyrosine kinase (TrKA) and insulin-like growth factor receptor, type 1 (IGF-1R) polypeptide as targeting agents useful in the claimed method. The p75 neurotrophin receptor (p75), neurotrophic receptor tyrosine kinase (TrKA) and insulin-like growth factor receptor, type 1 (IGF-1R) polypeptides are representative of a genus of polypeptides which share the biological characteristic of being expressed on the surface of tumor cells, including drug-resistant tumor cells. One skilled in the art would recognize that other compounds of the invention which include monoclonal antibodies directed to polypeptides expressed on the surface of tumor cells, including drug resistant tumor cells would be useful in the method of claim 35. As such, the Applicants submit that the application provides written description of the functional properties of such antibodies such that, at the time of filing, the Applicants demonstrated possession of a genus of monoclonal antibodies which selectively binds a polypeptide expressed on tumor cells, including a drug-resistant tumor cells claimed within the meaning of 35 U.S.C. §112, first paragraph. Accordingly, the Applicants believe that claims 35, 38 and 39 are in condition for allowance as they are in compliance with the written description requirement of 35 U.S.C. §112, first paragraph.

Claim Rejections -35 U.S.C. § 102

The Examiner rejected claim 35-37 pursuant to 35 U.S.C. §102(b) as allegedly anticipated by Kopecek *et al.*, U.S. Pat. No. 5,258,453 (1993) ("the '453 patent"). The Applicants traverse the rejection of these claims under 35 U.S.C. § 102(b) because this rejection is mooted by the amendment of claim 35 and cancellation of claims 36-37 by present amendment. Specifically, the Applicants have amended claim 35 to recite a method directed to a method of treating a patient with a tumor comprising drug-resistant tumor cells mediated by p-glycoprotein pump, by administering a compound which has a formula W-Z-X, wherein the

compound comprises a monoclonal antibody as a targeting agent. This method is neither taught or enabled by the '453 patent.

As noted above, claim 35, as amended, is directed to a method of treating a patient with a tumor comprising drug-resistant tumor cells mediated by p-glycoprotein pump, by administering a compound to the patient which has a formula W-Z-X. The claim recites that X is a chemotherapeutic agent (doxorubicin or paclitaxel); W is a monoclonal antibody which selectively binds to a polypeptide expressed by the tumor cells; and Z is a breakable linker which covalently links W and X together, wherein said W, when linked to Z, remains available for binding to the tumor cells, the breakable linker being cleavable in the cells for releasing X into the tumor cell. The release of X into the tumor cells is cytotoxic to the tumor cells thereby treating the patient.

The Examiner did not give patentable weight to the fact that the '453 patent did not teach a method directed to multi-drug resistant tumors mediated by p-glycoprotein pump because the recitation of drug-resistance mediated by p-glycoprotein pump was only recited in the preamble of the unamended claim 35. The Applicants have amended claim 35 such that the method recites the term "tumor cells, including drug-resistant tumor cells mediated by p-glycoprotein pump" in the body of the claim. The Applicants respectfully request the Examiner give patentable weight to the recitation of claim 35 to a method directed to treating "tumor cells, including drug-resistant tumor cells mediated by p-glycoprotein pump" in light of the teachings of the '453 patent. The Applicants believe that claim 35 as amended and claims 38 and 39 are in condition for allowance as they are directed to a method of treating a patient with a tumor comprising drug-resistant tumor cells mediated by p-glycoprotein pump, by administering a compound to the patient which has a formula W-Z-X which was not expressly or inherently anticipated by the teachings of the '453 patent.

The '453 patent is directed to compositions of "cancerous tissues in warm-blooded animals containing both an anticancer drug and a photoactivatable drug attached to copolymeric carrier." ('453 patent, abstract; emphasis added). The method of claim 35 of the instant application is not directed to the use of compositions which contain a photoactivatable drug element. The '453 patent further provides for compositions wherein the composition is "a mixture of copolymeric carriers wherein one copolymeric carrier has attached an anticancer drug and the other copolymeric carrier has attached a photoactivatable drug...." ('453 patent, abstract). "The polymer may optionally contain a targeting moiety." ('453 patent, abstract). One targeting mechanisms is to "bind the polymeric drug to an antibody which is recognized by those

cells which have the appropriate antigentic receptors." ('453 patent, column 4, lines 29-32). The '453 patent provides no specific teaching of how an antibody conjugate would be prepared or example of an antibody conjugate or specific teaching with respect to which molecule(s) an antibody conjugate should be directed. The '453 patent provides no working example of an antibody-directed chemotherapeutic copolymer compound. Further, the Examiner has agreed that the '453 patent does not expressly teach by-passing tumor resistance mediated by p-glycoprotein pump which is the basis for multiple drug resistance in tumors. (Office Action at page 10, line 23-24.). Taken together, the '453 patent fails to provide an enabling disclosure for the method of treatment of amended claim 35.

The Examiner alleges that the mechanism of cell entry by the macromolecule *via* pinocytosis is the same as claimed and is thus a characteristic which is inherent in all the compounds of the '453 patent. However, the Applicant notes that the studies presented by Minko *et al.*, which are presented in support of this notion, are based on the use of HPMA-copolymer-adriamycin conjugate compared with free adriamycin in adriamycin sensitive and adriamycin resistant human ovarian cancer cell lines. These model compounds are structurally distinct from the compounds of the invention as there is no targeting agent present. In light of the fact that "endocytosis can be a highly specific mechanism" (Minko *et al.*, at page 230, ¶3) the Applicants respectfully submit that the Examiner has failed in his burden to demonstrate that this "allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990); see generally MPEP §2112.

CONCLUSION

On the basis of the foregoing amendments, Applicants respectfully submits that the pending claims are in condition for allowance and respectfully request the same. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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Michel Morency, Reg. No. 50,183
James F. Ewing, Reg. No. 52,875
Attorneys for Applicants
Foley & Lardner LLP.
111 Huntington Avenue, 26th Fl.
Boston, MA 02199
Tel. 617-342-4000
Fax. 617-342-4001